forth at this time in response to rejection of the claims. Favorable consideration of the following comments relative to the outstanding rejections as they may apply to the present claims is respectfully requested for the reasons that follow.

An amended declaration was filed in the case on July 31, 2001. The above amendment to the specification likewise amends the claim of priority in the case.

Rejections Under 103(a)

Claims 16-23 and 28 are rejected under 35 U.S.C. §103(a) as being unpatentable over Jellis et al. in view of Russell et al., Druker et al., and Kaufman. Applicant respectfully traverses.

Jellis et al. concerns a phage display library and discloses unique nucleic acids encoding approximately $1.5x10^8$ unique peptides of 20 amino acids fused to coat proteins for display on the surface of phage particles. The emphasis in Jellis is the creation of unique peptides with minimal amino acid bias. Expression of random peptides in a retroviral vector is not disclosed by Jellis.

Druker et al. disclose a small collection of retroviruses with inserts encoding polyoma middle T antigens having point mutations. Druker demonstrates that the polyoma middle T antigen inserts can be expressed in a retroviral system, but does not disclose nor suggest that random peptides can be expressed in a retroviral system.

Kaufman is a general reference about a variety of mammalian expression vectors. Kaufman teaches that retroviral vectors can be used to transduce genes into a variety of host cell types, and that genes so introduced may incorporate into the host genome. Kaufman does not teach or suggest that retroviral vectors can be used to express random peptides.

Kaufman, in fact, teaches away from the combination of random peptides for expression in a retroviral vector. Kaufman states that expression from retroviral vectors is low, that there are problems w/RNA splicing etc., and that different DNA sequence inserts may impair propagation of expression, resulting in variable success.

Russell, et al. is concerned with the presentation of a non-viral protein moiety, particularly an antibody fragment with predetermined affinity for a given hapten, as a component of a fusion protein with a viral glycoprotein on the surface of retroviruses. Russell et al. is solely concerned with "display packages", e.g. viruses that contain fusions of non-viral polypeptides to "at least part of a glycoprotein and displayed on the external surface of the particle." (Col. 11, lines 64-66).

As stated in the MPEP at §2143, in order to support a *prima facie* case of obviousness under 35 U.S.C. §103(a), the prior art, either individually or in combination, must satisfy the following three elements:

1) there must be some motivation or suggestion, either in the references or in the knowledge available to one skilled in the art, to modify or combine the references to practice the claimed invention; and

2) there must be a reasonable expectation of success; and

3) the prior art references when combined must teach or suggest all of the claim limitations.

In view of these requirements, Applicant respectfully submits that the cited prior art references do not render the present invention obvious.

First, the Examiner asserts that the motivation to combine or modify the cited references in order to practice the instant invention is provided by a desire to create a single library with the hypothetical utility set forth by Russell et al. as well as utility in a screening method and a method of stable transformation. Applicant disagrees.

The Examiner's citation of Russell for motivation (column 16, lines 62-64) must be taken in the context in which Russell meant: that retroviral display packages (e.g. those containing fusions to glycoproteins) could be used analogously to phage display libraries. This, however, does not suggest retroviruses encoding random peptides not fused to retroviral glycoproteins.

In addition, as acknowledged by the Examiner, Jellis et al. does not disclose libraries of retroviruses or cells containing the libraries. Furthermore, it is not certain

from Jellis that random nucleic acid inserts will successfully encode novel peptides in a retroviral system. Druker does not add any motivation. Kaufman does not add any motivation for the creation of random peptide libraries, and in fact teaches away from such a library. Kaufman states that expression in retroviral-based vectors has met with variable success due to "problems with RNA splicing and mRNA translation" and because "insertion of different DNA sequences may impair propagation or expression of the recombinant retrovirus." (p. 495, 2nd column).

To summarize, none of the cited references, taken alone or in combination, provide the motivation to make retroviral random peptide libraries.

Even assuming, arguendo, that the motivation exists, there is no reasonable expectation of success. Kaufman, as discussed above, teaches away from the combination of references. Additionally, Russell et al. teach away from the present invention, and in particular, from retroviral libraries. Russell et al. suggest hypothetical uses for retroviral peptide display libraries, but temper their suggestions based on quantitative limits they foresee for the technology. Particularly, Russell et al. concede at column 17 line 9:

> The theoretical maximum achievable retroviral display library size does not compare favorably with the theoretical maximum size of a bacteriophage display library. It is therefore unlikely that retrovirus display libraries will challenge the established applications of phage display libraries such as in vitro antibody selection and affinity maturation.

Essentially Russell et al. suggest that retroviral peptide display libraries analogous to bacteriophage peptide display libraries cannot be synthesized. Attempts to do so would in their opinion result in a less pluralistic population of viral display particles which would likely not be of the same use as bacteriophage libraries. In this way, Russell et al. teach away from retroviral libraries comprising large numbers of randomized nucleic acids encoding a plurality of peptides. This teaching is furthered in the specification, where examples suggest that useful peptides be first identified in bacteriophage libraries

and subsequently used in retroviral display particles, rather than identified in retroviral libraries themselves.

In the absence of scientific support for the feasibility of arriving at the retroviral libraries posited by Russell et al., and given the teaching away from the instant invention by both Kaufman and Russell et al., the reasonably skilled artisan would not have a reasonable expectation of success in arriving at the instant invention given the cited references and knowledge available in the art at the time of filing.

Rejection concerning Nilsson

Claims 16-28 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Jellis et al. in view of Russell et al., Druker et al., Kaufman, and Nilsson et al. Applicant respectfully traverses.

Jellis et al., Russell et al., Druker et al., and Kaufman are discussed *supra*.

Nilsson et al. teaches the construction of fusion proteins for a variety of purposes. However, Nilsson et al. does not cure the defects of Jellis, Russell, Druker and Kaufman.

The Examiner states that it would be *prima facie* obvious to combine the teachings of Nilsson with the other references, based on Nilsson's teachings that fusion proteins can be constructed for a variety of reasons. However, Jellis, Russell, Druker and Kaufman do not provide adequate suggestion to combine their teachings to obtain the claimed invention, as discussed above. Nilsson does not cure the deficiencies of these references, and therefore, the combination of Nilsson with Jellis, Russell, Druker and Kaufman cannot provide for a prima facie case of obviousness.

The Examiner states that one skilled in the art "would readily be able to combine teachings of fusion peptides. . . with teachings regarding retroviral vectors." Applicant respectfully reminds the Examiner that the mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. *In re Mills*, 916 F.2d 680 (Fed.Cir. 1990). Additionally, a statement that modification of the prior art to meet the claimed invention

would have been well within the ordinary skill of the art because the references teach hat all aspects of the claimed invention were individually known is not sufficient to establish a *prima facie* case of obviousness without some objective reason to combine the teachings of the references. *See Ex parte Levengood*, 28 USPQ2d 1300 (Bd.Pat.App. & Inter. 1993); MPEP §2143.01.

Applicant submits that motivation or suggestion to combine or modify the cited references to practice the claimed invention is not provided by the references or by knowledge in the art, and that a reasonable expectation of success in arriving at the instant invention is not provided. Accordingly, Claims 16-28 are not obvious under 35 U.S.C. §103(a), and Applicant requests withdrawal of the rejections.

Rejection under 35 U.S.C. § 112, first paragraph

Claim 29 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventor, at the time the application was filed, had possession of the claimed invention.

Claim 29 is drawn to a library of cells intracellularly expressing randomized polypeptides. Applicant respectfully submits that the claim has support throughout the specification. At page 10, lines 21-22, it states, "the randomized expression product-containing region could be contained within a cytoplasmic region...." At page 37, lines 14-18, it discusses a screen for "intracellular peptide activators" of a metastasis suppressor gene. At page 40, lines 28-31, the specification discusses screening "intracellular peptides" for agents that "block the expression or function of ... oncogenes...." The title of the application itself points to screening for "intracelluar effector peptides." Applicant respectfully submits that the claim is described in the specification and requests, therefore, that the rejection be withdrawn.

CONCLUSION

Applicant respectfully requests favorable consideration of the preceding arguments and acceptance of the claims as currently pending. If the Examiner feels there are further unresolved issues, the Examiner is respectfully requested to phone the undersigned at (415) 781-1989.

Respectfully submitted,

FLEER HOHBACH TEST
ALBRITTON & HERBERT LLP

Robin M. Silva
Reg. No. 38,304

Four Embarcadero Center, Suite 3400
San Francisco, CA 94111-4187
Telephone: (415) 781-1989

APPENDIX:

16. (Amended) A molecular library of retroviruses comprising at least 10^4 different randomized nucleic acids encoding a plurality of randomized peptides.

17. (Amended) A molecular library of retroviruses according to claim 16 comprising at least 10^5 different randomized nucleic acids encoding a plurality of randomized peptides.

18. (Amended) A molecular library of retroviruses according to claim 16 comprising at least 10^6 different randomized nucleic acids encoding a plurality of randomized peptides.

19. (Amended) A molecular library of retroviruses according to claim 16 comprising at least 10^7 different randomized nucleic acids encoding a plurality of randomized peptides.

20. (Amended) A molecular library of retroviruses according to claim 16 comprising at least 10^8 different randomized nucleic acids encoding a plurality of randomized peptides.

21. (Amended) A cellular library of mammalian cells containing a molecular library of retroviral constructs, said molecular library comprising at least 10^4 different randomized nucleic acids encoding a plurality of randomized peptides.

22. A cellular library according to claim 21 wherein said constructs are integrated into the cellular genome.

23. A molecular library of retroviruses according to claim 16, wherein said nucleic acids further encode a fusion partner.

24. A molecular library of retroviruses according to claim 23, wherein said fusion partner comprises a targeting sequence.

25. A molecular library of retroviruses according to claim 23, wherein said fusion partner comprises a rescue sequence.

26. A molecular library of retroviruses according to claim 23, wherein said fusion partner comprises a stability sequence.

27. A molecular library of retroviruses according to claim 23, wherein said fusion partner comprises a dimerization sequence.

28. A molecular library of retroviruses according to claim 16, wherein said randomized nucleic acids are biased in their randomization.

29. A cellular library of mammalian cells containing a molecular library of retroviral constructs, said library of cells intracellularly expressing at least 10^4 randomized peptides.

30. (New) A cellular library of mammalian cells containing a molecular library of retroviral constructs, said library of cells intracellularly expressing at least 10^4 randomized peptides, wherein said each of said peptides is linked to a fusion partner.

31. (New) A cellular library according to claim 30, wherein said fusion partner comprises a rescue sequence.